DOI:10.1111/j.1477-2574.2010.00181.x HPB

ORIGINAL ARTICLE

Pretreatment assessment of hepatocellular carcinoma: expert consensus statement

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Abstract

Staging of hepatocellular carcinoma (HCC) is complex and relies on multiple factors including tumor extent and hepatic function. No single staging system is applicable to all patients with HCC. The staging of the American Joint Committee on Cancer / International Union for Cancer Control should be used to predict outcome following resection or liver transplantation. The Barcelona Clinic Liver Cancer scheme is appropriate in patients with advanced HCC not candidate for surgery. Dual phase computed tomography or magnetic resonance imaging can be used for pretreatment assessment of tumor extent but the accuracy of these methods remains poor to characterize <1 cm lesions. Assessment of tumor response should not rely only on tumor size and new imaging methods are available to evaluate response to therapy in HCC patients. Liver volumetry is part of the preoperative assessment of patients with HCC candidate for resection as it reflects liver function. Preoperative portal vein embolization is indicated in patients with small future liver remnant (≤ 20% in normal liver; ≤ 40% in fibrotic or cirrhotic liver). Tumor size is not a contraindication to liver resection. Liver resection can be proposed in selected patients with multifocal HCC. Besides tumor extent, surgical resection of HCC may be performed in selected patients with chronic liver disease.

Keywords

consensus conference, staging, portal vein embolisation, liver function, hepatocellular cancer, hepatoma, surgery, chemotherapy, radiotherapy, chemoembolization

Received 14 April 2010; accepted 19 April 2010

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Staging of hepatocellular carcinoma

Background

The construction of an internationally accepted and preferentially used staging system for hepatocellular carcinoma (HCC) has proven to be a daunting task.[1] Estimating prognosis for patients with HCC is extremely complex because prognosis depends not just on tumor related factors and the anatomic extent of disease but also on liver function, patient factors, treatment efficacy and interactions between them[2,3] (table 1). Liver function is likely the most important predictor of survival since the majority of patients with HCC have end stage liver disease whereas tumor extent and tumor directed therapy have limited influence on survival.[1,4,5] In patients without, or limited, liver disease, quality and type of treatment are more important predictors of outcome than tumor related factors.[4,6]

In 1999, the European Association for Study of Liver Disease (EASL) proposed a staging system which included four variables: anatomic tumor stage, degree of liver dysfunction, general

Proceedings of the Consensus Conference on Multidisciplinary Treatment of Hepatocellular Carcinoma sponsored by the American Hepato-Pancreato-Biliary Association and co-sponsored by the Society of Surgical Oncology and the Society for Surgery of the Alimentary Tract and the University of Texas M. D. Anderson Cancer Center held in Orlando, FL, USA; January 21, 2010.

Table 1 Predictive factors of outcome in HCC

Patient factors	General medical conditions Performance Status Quality of life score
Tumor factors	Number, size, total tumor volume Histopathologic grade Vascular invasion DNA aneuploidy (DNA index) Genotype VEGF levels Serum AFP
Liver factors	Child Pugh score MELD score Fibrosis score Active inflammation Functional hepatic reserve Maximal removal rate of glycolated human serum albumin (GSA-Rmax) Protein induced by vitamin K absence/antagonism II (PIVKA-II serum levels)
Etiology of liver disease	Alcohol Hepatitis B Hepatitis C
Interactions between patient factors, tumor factors and treatment efficacy	

Table 2 HCC Staging Systems

Clinical	Okuda IHPBA (International Hepato-Pancreato-Biliary Association) CLIP (Cancer of the Liver Italian Programme Score) BCLC (Barcelona Clinic Liver Cancer) Revised BCLC CUPI (Chinese University Prognostic Index) American Liver Tumor Study Group modified Tumor-Node-Metastasis classification. (ALTSG) Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire (GRETCH)
Pathological staging systems	American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) Liver Cancer Study Group of Japan (LCSGJ) staging system Japanese Integrated Staging (JIS) score (includes the LCSGJ) Modified JIS New Liver Cancer Study Group of Japan TNM Early HCC prognostic score Tokyo score
Transplant staging systems	UNOS modified TNM staging system UCSF extended criteria Pittsburgh scoring system

condition of the patient and treatment efficacy.[5] Since then, a number of new staging systems have been developed to improve selection for therapies and predict survival.[7] However, there is no universally accepted staging system that enables investigators to compare treatment results across institutions and regions.[8]

The problem of using multiple staging systems

The first AHPBA and AJCC consensus conference on staging for HCC in 2003 recognized that no single staging system fulfilled all the needs of physicians treating HCC.[9] The group recommended the use of the Cancer of the Liver Italian Program (CLIP) staging system for prognosis stratification and treatment guidance in nonsurgical patients with advanced HCC and/or liver disease and use of the 6th edition of the AJCC/UICC TNM for patients who qualify for liver resection and liver transplantation. The AHPBA consensus group agreed with the EASL expert panel that HCC staging systems should combine liver disease, general health and tumor factors as features of a system to provide guidance for patient therapy, estimate prognosis, and save health care resources.[9] To date, the problems created by the use of multiple staging systems for HCC are not resolved. At the time of the 2010 AHPBA HCC consensus conference, there were 18 HCC staging or scoring systems in use around the world (table 2). The plethora of staging systems is related principally to two issues. First, no single staging system predicts accurately outcomes for all HCC patients. Staging system performance is highly variable because it depends upon many factors including patient demographics, treatment, type and extent of liver disease and stage of disease.

Secondly, improved understanding of the natural history of HCC, its response to various treatments and identification of new biologic markers that may predict outcomes have resulted in the rapid evolution of staging systems.

The importance of accurate tumor staging prior to treatment

Staging HCC is difficult, thus leading to staging inaccuracies and challenges when trying to compare treatment and study outcomes. For instance, difficulty discriminating early HCC from enhancing regenerative nodules smaller than 2 cm has led to some patients being falsely labeled with HCC. Tumor related factors such as microvascular invasion and molecular signatures or DNA analyses, which are powerful predictors of outcome, can be used for staging, but depend upon tissue being available for analysis. However, many patients are not subjected to biopsy or tumor excision prior to treatment. Diagnostic laparoscopy and laparoscopic ultrasound increase the detection of multi-focal tumors, portal hypertension and macrovascular invasion leading to a change in tumor stage in up to 25% of patients.[10] Whole body positron emission tomography imaging with C^{11}-acetate can be useful to detect extra hepatic metastatic HCC.[11] Thus, HCC staging can vary widely based on the modalities used during the pretreatment evaluation. This leads to erroneous treatment decisions and ultimately to misleading and inaccurate treatment results – especially for non operative therapies where anatomic and biologic markers are not obtained prior to treatment. The establishment of guidelines for optimal staging strategies, therefore, should allow for more precise comparisons between differing treatment regimens.

Establishing the relative value of different staging systems

There is consensus among experts that a HCC staging system should be retrospectively and prospectively validated in the patient populations where its use is proposed.[1,4,7,9] Recent studies comparing HCC staging systems to one another evaluated the ability to discriminate outcomes in particular patient populations subjected to specific therapies.[12–21] Most staging systems studied perform poorly when the study population includes a cohort of patients with a wide spectrum of diseases and tumor stages. What has emerged from these studies is an appreciation that the discriminatory performance of various staging systems appears to be treatment, stage and region specific.[20–22] For example, the 6th edition of AJCC TNM staging[16,23] and the early prognosis score[12,24] perform well for patients with early stage disease undergoing liver resection or transplantation,[12,16] whereas CLIP is predictive of outcome in French patients in the palliative setting.[25]

Does tumor size matter?

The use of tumor size as a criterion for HCC staging systems remains controversial. The 6th edition of AJCC TNM staging found that tumor size alone did not predict survival after surgical resection whereas advanced liver fibrosis did.[26] Conversely, other studies find size, even in early HCC, a reliable discriminator for survival.[12,24] For example, up to 25% of tumors less than 2 cm have vascular invasion and poor survival after resection, ablation or transplantation.[12,24,27] Likewise, since the adoption of the Mazzaferro staging criteria, the use of tumor size to qualify patients for liver transplantation remains contentious.[28] While the risk of vascular invasion increases with size, some tumors can grow quite large without vascular invasion and these patients do well after transplantation.[29] This led to the development and use of expanded criteria for selecting patients for liver transplantation,[30,31] whereas other groups have explored the benefit of neoadjuvant tumor reduction strategies prior to transplantation.[32]

The emergence of biologic factors as important prognostic variables in HCC

Recent studies show tumor biology and non tumor liver factors are powerful predictors of outcome independent of tumor size. Kaibori *et al.* reported that limited pre treatment hepatic functional reserve in Japanese patients, measured by maximal extraction of glycolated serum albumin, independently predicts early tumor recurrence and short survival even in patients with tumors less than 2 cm.[27] Some small HCCs have high metastatic potential as shown by gene expression assessment through microarrays and have an incidence of vascular invasion as high as 25%.[33] Jonas *et al.* recently reported that increased tumor DNA aneuploidy, expressed as an index, is a more powerful prognostic indicator than tumor size, Milan Criteria, or vascular invasion in cirrhotic patients with HCC following liver transplantation.[34] Poon and colleagues reported that pretreatment serum VEGF levels independently predicted overall and recurrence-free survival following radiofrequency ablation.[35] Collectively, these studies suggest liver or tumor-related factors in patients with cirrhosis and HCC that may influence the risk for recurrent disease.

Consensus statement

1. Based on current knowledge and experience, no single staging system is applicable to all patients with HCC.
2. The use of regional staging system is discouraged because it precludes comparison between centers.
3. In medical patients with advanced liver disease who are not candidates for liver transplantation or resection, the Barcelona Clinic Liver Cancer (BCLC) classification is appropriate.
4. There is significant heterogeneity within stage B and C of the BCLC classification, thus resection may be considered for some of these patients. Overall, BCLC criteria provide a reasonable guide for treatment considering the caveat regarding stage B and C patients.
5. The AJCC/UICC classification is valid for HCC staging based on single and multicenter studies in the West and East, including Japan and China for patients undergoing liver resection. It is useful in patients with a normal liver or chronic liver disease when coupled with the fibrosis score.

6. Report pathological outcomes using the AJCC/UICC system following resection or liver transplantation.
7. In the future, incorporation of recently described biomarkers (VEGF plasma level and DNA index) may improve preoperative staging.

Optimizing pretreatment imaging of HCC

Background

The incidence of HCC has doubled over the past 2 decades in the US, currently estimated between 8,500–11,500 / year, and is predicted to increase over the next years mostly related to an increase in chronic viral hepatitis C infection.[36,37] Consequently, radiologists will encounter HCC during routine imaging with increasing frequency. The hypervascular nature of HCC makes dual (arterial and portal venous phases) or three-phase imaging (arterial, portal venous and delayed phases) with dynamic intravenous contrast injection a critical feature for the detection and characterization of this tumor whether using computed tomography (CT) or magnetic resonance imaging (MRI). Additionally, arterial phase imaging with multidetector row CT (MDCT) or MRI allows a clear image of the vascular supply of the tumor and to the liver. This is critical in patients who are candidates for transarterial chemoembolization (TACE), surgical resection or liver transplantation.

Multidetector row computed tomography

MDCT is widely used for the detection of HCC before liver resection or transplantation.[38] MDCT has several advantages including rapid image acquisition, wide availability, high resolution images, and multiphasic scanning. These features result in good accuracy for HCC detection.[38,39] However, MDCT is limited by the radiation dose,[40] which is non negligible in this patient population where repeat imaging is common. In theory, double arterial phase imaging with MDCT should improve HCC detection. However, two prior studies[39,41] did not show improved HCC detection using MDCT compared to a conventional single arterial acquisition. Murakami *et al.*[42] used a triple arterial phase acquisition (at 20, 30 and 40 sec. after administration of contrast) with MDCT for HCC detection, and showed that the second arterial phase showed the best sensitivity compared with the early and late arterial phases for HCC detection (mean area under the receiver operating curve: 0.84 vs. 0.56 (early) and 0.62 (late arterial phase). In our institutions, we use 16- and 64-MDCT with a single arterial phase based on the bolus track method.

Magnetic resonance imaging

Recent technological advances in hardware and software, together with the development of a variety of contrast agents, have allowed liver MRI to be considered the most accurate noninvasive imaging technique for HCC detection. MRI lacks ionizing radiation, offers higher contrast resolution and the possibility of performing multiparametric imaging, combining T1, T2, and diffusion-weighted imaging with dynamic multiphasic imaging. State of the art MRI now offers routinely thin 3D T1-weighted dynamic acquisitions.[43] In addition, 3T MRI offers higher spatial resolution compared to 1.5T MRI, due to improved signal to noise ratio.[44,45] With the use of extracellular[46,47] or liver-specific contrast agents such as superparamagnetic iron oxide (SPIO) particles[48] or gadobenate dimeglumine,[49] MRI has a similar to higher diagnostic accuracy compared to CT for HCC detection. Kim *et al.*[48] compared the accuracy of SPIO-enhanced MRI and 16-MDCT, and found higher AUC for SPIO-enhanced MRI (0.90) compared to that for MDCT (0.82), without significant difference. They found a trend toward increased sensitivity on both a per-lesion and a per-patient basis for SPIO-enhanced MRI (84.7% and 94.7%, respectively) compared with MDCT (76.9% and 88.6%, respectively). Two studies[46,47] using extracellular agents showed better detection of HCC nodules with MRI compared to CT. Burrel *et al.*[47] showed a sensitivity per-lesion of MRI of 76% vs. 61% for CT. However, sensitivity of MRI for detection of small lesions is still low. In the study by Burrel *et al.*,[47] 100% of nodules > 2 cm were detected, compared to 84% for nodules between 1–2 cm, and 32% for nodules less than 1 cm. A recently FDA approved liver-specific gadolinium contrast agent called gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA or gadoxetic acid disodium, Eovist (US) or Primovist (Europe, Asia) Bayer Healthcare) produces both dynamic and liver-specific hepatobiliary images.[50–60] This contrast agent is highly liver-specific, with approximately 50% of the injected dose taken up by functioning hepatocytes and excreted in bile, compared with an uptake of 3–5% for gadobenate dimeglumine.[60] Results for detection of HCC are so far promising.[52] Few investigators have used SPIO particles with or without the combined use of Gd-DTPA for HCC. Using both Gd-DTPA and SPIO, Bhartia *et al.*[62] demonstrated 78% sensitivity for detection of HCC.

Advanced MRI methods

These include image subtraction, diffusion-weighted imaging (DWI), perfusion-weighted imaging (PWI) and magnetic resonance elastography (MRE). Image subtraction is essential to assess enhancement of T1 hyperintense liver nodules and for the estimation of tumor necrosis after TACE.[48,63] DWI can detect tumor necrosis after TACE without the use of contrast media and can be used to follow patients after TACE. DWI, PWI and MRE show promising results for detection of background liver fibrosis and cirrhosis.[44,64,65] Finally, specific MRI sequences can be used to accurately detect fat and iron in the liver and in liver nodules.[66]

Consensus statement

1. The choice between dual-phase CT and MRI depends on local expertise and availability. The utility of CT is limited by the radiation dose. MRI has the best performance characteristics for the detection of HCC. Ultrasound, particularly contrast enhanced, could be useful for HCC screening when this expertise is available.

2. While MRI is superior to CT for HCC detection, both have limited sensitivity and specificity for the detection of lesions < 1 cm.
3. New MR liver specific agent (Gd-EOB-DTPA) is promising for HCC detection and characterization.
4. Assessment of treatment response should not rely on lesion size anymore. Image subtraction and diffusion-weighted MRI are new emerging markers of the adequacy of local/loco-regional and systemic treatments.
5. Background liver fibrosis and cirrhosis may be assessed with functional MRI but this is still under investigation.

The role of portal vein embolization in preparation for hepatic resection for HCC

Initially performed to prevent portal tumor extension of HCC,[67] portal vein embolization (PVE) now is a well established method to increase the volume and function of the non-embolized liver prior to major hepatic resection. PVE leads to an increase in future remnant liver (FLR) volume which is associated with improved liver function measured by increased biliary excretion,[67,68] technetium-99m-galactosyl human serum albumin uptake[69] and by significant improvement in the postoperative liver function tests following PVE.[70] PVE is used prior to extended hepatectomy in patients without, or with limited liver disease and before major hepatectomy in well compensated cirrhotic patients.[71–74] Meta-analysis of 37 studies including over 1,000 patients shows the safety of PVE (morbidity 2.2%, mortality 0%), an increase in FLR volume, and the ability to perform major resection with very low risk of transient liver insufficiency (2.5%) or mortality from liver failure (0.8%) despite extensive resections.[75] FLR volume correlates with FLR function, and importantly, the volume change after PVE predicts functional outcome after resection.

Indications for PVE depend on factors that impact on the volume of liver remnant needed for adequate post-hepatectomy liver function. The absence or presence of underlying liver disease and its severity impact on the need for PVE. Additional factors include patient size (large patients require larger liver remnants than smaller patients) and the extent and complexity of the planned resection. One must consider all these factors in the setting of the patient's age and comorbidities that may influence regeneration, such as diabetes. The volumetry should integrate assessment of the actual FLR volume with patient size, so that the standardized FLR volume expressed as a percentage of total liver volume (%TLV) is used to determine the need for PVE. FLR volume determined by three-dimensional CT imaging is standardized, typically to body surface area (BSA) or an estimated total liver volume based on a BSA formula to generate a 'standardized' FLR volume (i.e. volume standardized to the patient).[70]

The volume limit for safe resection likely varies from patient to patient. Current guidelines evolved following careful analysis of outcomes after major hepatectomy. In patients with a normal liver, PVE is indicated when the standardized FLR volume is ≤ 20%, based on an analysis of complications in 42 patients, all of whom had normal underlying liver and underwent right trisectionectomy.[76] The complication rate, intensive care unit stay and hospital stay were prolonged in patients with a FLR volume ≤ 20% compared to those with >20%. A subsequent study in patients with normal liver confirmed this cutoff and showed that a FLR volume increase > 5% indicates a low risk for liver failure after resection.[77] Findings from two larger datasets validated these findings.[78,79]

Data from 301 consecutive right trisectionectomies in patients with normal liver confirmed a clear correlation between postoperative liver insufficiency and FLR volume.[78] Direct comparison of patients with small (≤20% of TLV), intermediate (20.1 – 30% of TLV) and large (≥ 30% of TLV) FLR volumes showed an increased risk for liver insufficiency (and postoperative death) in patients with small FLR volumes.[78] Patients with pre-PVE FLR volume ≤20% whose liver volumes increased to >20% post-PVE underwent resection with complication, liver insufficiency, and liver failure rates statistically equivalent to those who had a native FLR volume > 20 or even > 30%. Their complication rate was significantly lower than those operated with FLR volume < 20%.[78] This study suggests that high risk, low FLR volume patients can be converted by PVE to low risk (higher FLR volume) patients.

Among patients with intermediate liver disease, such as fibrosis without cirrhosis, a larger FLR has been proposed (FLR ≤ 30% of the TLV) to improve the safety of major resection.[80,81] Similarly, a larger FLR (>40% TLV) has been advocated for patients with cirrhosis. Major resection in patients with cirrhosis is feasible when liver function is preserved and portal hypertension (manifest as splenomegaly, periesophageal varices and platelet count < 100,000/microliter) is absent. PVE is indicated in most cirrhotic patients where right hepatectomy is planned,[71] or when the FLR is ≤ 40% of the TLV.[72,74] Leaving a smaller volume in patients with cirrhosis results not only in liver insufficiency, but death from liver failure after resection.[74]

A prospective, alternate allocation study[71] demonstrated that PVE is beneficial before right hepatectomy in patients with cirrhosis. A significant decrease in postoperative complications, duration of intensive care unit and total hospital stay occurred in cirrhotic patients who underwent right hepatectomy after PVE versus those who underwent right hepatectomy with cirrhosis without PVE. Patients in the PVE group had a mean FLR of 35% – an indication for PVE based on the work of Kubota *et al.*[72] described above. The proportion of patients with one or more complications, incidence of pulmonary complications, ascites and liver failure was lower in the PVE group (all $p < .05$). These authors also reinforced the initial finding of Hirai *et al.*[69] that FLR growth in response to PVE is a predictor of favorable postoperative outcomes.

A recent study compared 21 patients who underwent major hepatectomy after PVE compared to 33 patients who underwent hepatectomy without PVE.[73] Overall complication rates were similar between groups, but the major complication rate in the non-PVE group was 35% compared to 10% in the PVE group

(p = .028). There were no perioperative deaths in the PVE group but six deaths (18%) in the non-PVE group (P = .038). Postoperative mortality was related to liver insufficiency leading to multiorgan failure in five; the sixth died with exacerbation of preexisting renal disease. The two patients in the non-PVE group who underwent preoperative volumetry did not experience complications. Importantly, oncologic outcomes in these patients with large and multifocal HCC were equivalent (5-year overall survival rate 72% with PVE versus 54% without PVE; 5-year disease-free survival rate 56% with PVE vs. 49% without PVE, both p = NS).[73]

Recently, the combination of TACE followed by PVE has been proposed as a method to optimize liver growth and tumor treatment.[82,83] Hypertrophy rates for TACE + PVE exceed hypertrophy rates for PVE only, likely because of occlusion of intratumoral arteriovenous shunts by TACE prior to PVE.[82] In addition, pathologic analysis showed a high response in the treated tumors after this combination of embolizations.[83] Though data are limited with this combined approach, it appears to be an extremely effective method of reducing risk and optimizing outcome for major resection in cirrhotic patients.

Contraindications to PVE include an adequate FLR based on the listed criteria and tumor invasion of the portal vein on the side for resection, as portal flow is already diverted. Relative contraindications include tumor extension to the FLR, uncorrectable coagulopathy, biliary dilatation in the FLR (if the biliary tree is obstructed, drainage is recommended), portal hypertension and renal failure.

In conclusion, PVE is an effective method to increase the volume and function of the FLR prior to major hepatectomy in a spectrum of patients with normal, diseased, and cirrhotic livers. With regard to patients with HCC and cirrhosis, PVE appears to dramatically decrease risk for liver insufficiency and death after liver resection, without negative impact on oncologic outcome. TACE with PVE is emerging as a potential method to further increase safety and improve outcomes following major resection for HCC.

Consensus statement

1. Volumetry to evaluate the FLR is indicated if major hepatic resection (resection involving more than four segments) is planned or if the patient has underlying liver disease.
2. Preoperative PVE is appropriate when the FLR volume is ≤20% of TLV in patients with normal liver; ≤30% of TLV in patients with liver injury; and ≤40% of TLV in patients with well compensated hepatic fibrosis or cirrhosis.
3. Imaging is indicated 3–4 weeks after PVE to reassess liver volume and degree of hypertrophy.
4. Resection is generally considered safest when FLR volume reaches the target (20% to 40% depending on liver disease as above), and degree of FLR hypertrophy is adequate (at least 5% increase in FLR volume in normal liver and 10% increase in FLR volume in cirrhosis).
5. Preoperative PVE is appropriate in patients with chronic liver disease who are candidates for major hepatectomy. TACE followed by PVE should be considered in patients with chronic liver disease who are candidates for major hepatectomy.
6. The benefits of PVE are clearly established prior to major hepatectomy in selected subsets of patients with and without chronic liver disease. There is no role for a randomized trial of PVE.

Defining criteria for resectability – tumor characteristics and liver function

Background

HCC is the leading cause of cancer death in Asia, and its incidence is rising in Western countries. Surgical resection remains an important potentially curative option. Currently, only 10–25% of patients with HCC are resectable at the time of presentation. HCC primarily occurs in the setting of underlying liver disease caused by chronic viral hepatitis infection, alcohol use, genetic disorders, or environmental exposures. Because most patients have underlying liver disease, pre-operative assessment of liver function plays a central role in determining resectability. In addition, various tumor-specific characteristics such as tumor size, number, and the presence of vascular invasion affect whether surgical resection is appropriate. In general, patients with preserved liver function and small tumors are candidates for resection. Similarly, patients with preserved liver function and large tumors are usually candidates for resection, but this depends on the location of the tumor(s) and the volume of the FLR. In contrast, patients with an anticipated small FLR or poor hepatic reserve have traditionally not been considered candidates for surgical resection. The selection of patients with HCC who should undergo surgical resection continues to evolve and remains a source of some debate.

Liver function considerations

The spectrum of underlying liver disease can range from non-bridging fibrosis to frank cirrhosis with associated severe fibrosis. Preoperative sampling / biopsy of the non-tumorous liver may occasionally be helpful in determining the extent of the chronic liver disease. Unfortunately, the variability of fibrosis throughout the liver is often a significant limitation in the preoperative assessment of fibrosis by a liver biopsy.[84] As such, routine biopsy of the non-tumorous liver is unwarranted and not recommended.

The most commonly employed system for evaluating liver function and the extent of cirrhosis is the Child-Pugh classification scheme. The Child-Pugh score is a composite score including three laboratory parameters (bilirubin level, albumin level, prothrombin time) and two clinical factors (presence or absence of ascites and encephalopathy). Surgical resection can be considered in Child-Pugh A and very selected Child-Pugh B patients.[85] However, while the Child-Pugh score is useful in assessing global liver function, there is heterogeneity within Child-Pugh classes and Child Pugh alone does not allow adequate selection of surgical candidates. The risk of perioperative mortality increases with the degree of hepatic functional impairment even in patients

with well-compensated cirrhosis. A pre-operative MELD value of greater than 10 has been shown to be associated a 90-day mortality rate approaching 15–20%.[86,87] In patients with well-compensated cirrhosis, the MELD score is another useful tool to select good candidates for major liver resection.

Other measures to evaluate hepatic metabolic function include indocyanine green (ICG) retention rate, galactose elimination, and aminopyrine clearance. Most experience with ICG comes from Japan because this test is not widely used in the West. Although retention rates at 15 minutes after intravenous injection of ICG (0.5 mg/kg) can be useful prior to minor resection in patients with cirrhosis, it provides an overall measurement of function and does not differentiate between the liver planned for resection and the anticipated liver remnant.

A number of groups have reported that the combination of cirrhosis and portal hypertension is a relative contraindication for resection of HCC.[1,3] More recently, others have reported acceptable results following resection of HCC in patients with portal hypertension and cirrhosis.[85,88] Selected patients with portal hypertension can have good outcomes after minor resection (≤two segments). On the other hand, patients with significant underlying liver disease who require a major liver resection are more likely to have significant postoperative morbidity and mortality. Consideration for preoperative portal vein embolization is appropriate and based on the size of the FLR.

Tumor characteristic considerations

Large HCCs – tumors with a diameter of 5 cm or more – are relatively common, especially when screening is not routine.[89] In particular, the incidence of large HCCs is especially high in patients under the age of 40 years. Patients with large HCCs are generally not considered candidates for liver transplantation or ablation.[28] Hepatic resection, therefore, remains the only tenable treatment option for these patients.[90] However, some have suggested that large tumor size should be a contraindication to liver resection.[91] Cited as contraindications are the technical challenges of the operation and the worse prognosis associated with larger tumors and the associated increased vascular invasion. More recent data suggest, however, that patients with large tumors or multi-nodular disease should be considered for surgical resection. When resecting HCC > 10 cm, overall and disease-free 5 year survival was reported to be 45% and 43%, respectively.[92] In a different series of 300 patients with HCC > 10 cm, the reported peri-operative mortality was 5% with the majority of patients having a major hepatic resection.[93] While overall survival was 25–30%, patients with a solitary large HCC without vascular invasion had a 5 year survival of 40–45%. In a third study, patients with large HCC without vascular invasion had a reported survival of >70%.[94] In aggregate, these data emphasize that resection of large HCCs is safe and the use of size alone to exclude patients from surgical consideration is unwarranted.

Multi-focal HCC is associated with a poor prognosis, recognized by its incorporation into most HCC staging and classification schemes. Five year survival rates in patients with compensated cirrhosis who undergo resection of multinodular HCC varies widely from 25% to 58% with recurrence rate ranging from 80 to 100%.[85,95,96] Liver transplantation is the best treatment option in patients with multinodular HCC and cirrhosis who meet transplant criteria. Liver resection also can be offered in a subset of patients with multinodular HCC outside the transplantation criteria with good outcomes. The primary problem is appropriate selection of patients with multinodular HCC since few predictive factors of survival have been identified. Ishizawa *et al.* showed that Child Pugh B status, a positive serology for hepatitis C virus and microvascular invasion were associated with a poor long term survival rate after resection in patients with multinodular HCC.[85] Thus, the heterogeneity of tumor size more likely suggests intrahepatic metastases and advanced disease in patients with multinodular HCC; patients with multiple lesions of different size have poor outcomes and are not good candidates for resection.[85,95,96]

Surgical resection for patients with HCC invading the portal vein and/or the hepatic veins remains controversial. The results of hepatic resection for HCC with major vascular invasion have been disappointing, with 5-year survival rates of 10–11%.[97] Ikai *et al.*[98] also reported that the degree of portal or hepatic vein invasion significantly affected survival. Patients with tumor thrombus distal to the second branch of the portal vein (Vp1) or in the second branch of the portal vein (Vp2) had a significantly longer survival than patients with tumor thrombus either in the first branch of the portal vein (Vp3) or in the portal trunk (Vp4). Similarly, patients with tumor thrombus in a tributary of the main hepatic vein (Vv1) had a better prognosis than patients with invasion of the main hepatic vein (Vv2). In the same study,[98] patients with Vp3 and Vv2 vascular invasion had 5-year median survival durations of 7% and 11%, respectively. Data from an international cooperative group[99] reported a 5-year survival rate of 10% for resected patients with Vp3 or Vv2 tumor thrombus, similar to the rates in earlier reports by Poon and Fan[97] and Ikai *et al.*[98] As such, while not a formal contraindication to surgery, the benefit of resection is limited to highly selected cases. In general, surgical resection in patients with vascular invasion with extension to the main portal trunk or vena cava is not likely to be beneficial.

Consensus statement

1. It is important to consider the severity of any underlying liver disease when assessing resectability. The MELD score is helpful for selecting patients with compensated cirrhosis as candidates for major hepatic resection. The indication for preoperative portal vein embolization is based on volumetric measurements of the FLR.
2. While minor resection is not contraindicated in selected Child-Pugh A patients with portal hypertension, the presence of ascites and a serum bilirubin > 2 mg/dL are contraindications for such resections. Major liver resection may be consid-

ered in patients with Child – Pugh A cirrhosis without portal hypertension and bilirubin serum level ≤ 1 mg/dL in patients without biliary obstruction. ICG R15, when available, can be useful for the selection of patients with advanced liver disease who are candidates for minor liver resection.

3. Strict tumor size criteria to consider resection are unwarranted. Large (>5 cm) tumor size is not an absolute contraindication for resection.
4. Patients with multi-focal tumors who have adequate liver function / FLR should be considered for resection. Patients with multi-nodular disease, however, have a particularly high risk of recurrence. As such, transplantation is a better option for patients with multinodular disease and chronic liver disease who meet Milan criteria.
5. While major vascular invasion of the ipsilateral hepatic or portal vein is not an absolute contraindication to surgery, the long-term benefit of resection for patients with main portal vein or caval tumor thrombus is very limited. Resection in these patients is considered a palliative procedure and is rarely indicated.

Acknowledgements

The authors particularly thank Ruth Haynes for editing.

Conflict of interest

None declared.

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